Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 30-34, 65-68, 74, 82-95, 186, 188-190, 206-212, and 214-234 are pending in the application, with claims 30, 31, 65, 186, and 214-216 being the independent claims.

Claims 30, 31, and 65 have been amended by (i) deleting the phrase "or β(1,4)-galactosyltransferase activity" and (ii) replacing the phrase "the Golgi resident polypeptide that provides the glycosyltransferase activity of said fusion polypeptide" with either "β(1,4)-N-acetylglucosaminyltransferase III" or "GnT III." The dependency of claim 74 has been amended. Support for these amendments can be found, *inter alia*, at page 7, paragraph [0014].

Claims 30, 31, and 65 have also been amended by indicating that the polypeptide produced by the host cell has increased Fc-receptor binding or effector function as result of the recited modification. Support for these amendments can be found, *inter alia,* at page 67, paragraph [0127].

New claims 214-234 are sought to be added. Support for new claims 214-216 is found, *inter alia*, at page 7, paragraph [0014] and at page 67, paragraph [0127]. Support for new claims 217-234 can be found, *inter alia,* in original claims 65-68, 73, 74, and 82-95; at page 7, paragraph [0014] of the specification as filed; and at page 67, paragraph [0127]. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. The Rejections

A. Rejection Under 35 U.S.C. § 102(b)

Claims 30-34, 65-67, 73, 74, and 82-95 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by PCT publication WO 99/54342 ("Umaña") as evidenced by Grabenhorst *et al. J. Biol. Chem. 274*:36107-36116 (1999) ("Grabenhorst") and Shields *et al. J. Biol. Chem. 277*:26733-26740 (2002) ("Shields").

Not in acquiescence to the rejection and solely in an effort to expedite prosecution, Applicants have amended the pending claims by indicating that the fusion polypeptide having β(1,4)-galactosyltransferase activity ("GalT") has the Golgi localization domain of a Golgi resident polypeptide selected from the group consisting of: mannosidase I ("Man I"), mannosidase II ("Man II"), β(1,2)-N-acetylglucosaminyltransferase I ("GnT I"), β(1,2)-N-acetylglucosaminyltransferase II ("GnT II"), and α1-6 core fucosyltransferase ("FT"). Applicants respectfully traverse this rejection as it may be applied to the currently pending claims.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. M.P.E.P. 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 361 (Fed. Cir. 1987)). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic v. Genentech, Inc.,* 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

The invention as presently claimed is directed to methods for modifying the glycosylation profile of polypeptides produced by mammalian host cells through the use of (i) a fusion polypeptide having β(1,4)-N-acetylglucosaminyltransferase III ("GnT III") activity and comprising the Golgi localization domain of a Golgi resident polypeptide other than GnT III or (ii) a fusion polypeptide having GalT activity and comprising the Golgi localization domain of a Golgi resident polypeptide selected from the group consisting of: Man I, Man II, GnT I, GnT II, and FT, and methods for producing polypeptides modified by the same fusion glycosyltransferases.

Applicants respectfully submit that Umaña does not mention (i) fusion polypeptides having GnT III activity and comprising the Golgi localization domain of a Golgi resident polypeptide other than GnT III or (ii) fusion polypeptides having GalT activity and comprising the Golgi localization domain of a Golgi resident polypeptide selected from the group consisting of: Man I, Man II, GnT I, GnT II, and FT, or methods for producing polypeptides modified by the same fusion glycosyltransferases. Therefore, Umaña does not teach each and every element as set forth in the pending claims.

In view of the above, it is respectfully requested that the rejection of claims 30-34, 65-67, 74, and 82-95 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

B. Rejection Under 35 U.S.C. § 103(a)

Claims 30-34, 65-68, 73, 74, 82-95, 186, 188-190, 195, and 206-212 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Umaña, Grabenhorst, and Shields in view of PCT publication WO 01/29242 A2 ("Russell") and Rabouille *et al. J. Cell. Sci. 108*:1617-1627 (1995) ("Rabouille"). Applicants respectfully traverse this rejection as it may be applied to pending claims.

1. Elements of a Prima Facie Case of Obviousness

In order to establish a *prima facie* case of obviousness, (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

The Supreme Court in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398, 82 USPQ2d 1385 (2007) *(KSR)*, noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), the Court stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex*, 550 U.S. at 735, 82 USPQ2d at 1396

The Examiner has the burden of establishing a *prima facie* case of obviousness.

2. Umaña

In rejecting the claims, the Examiner asserts that "Umana et al suggest that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the *trans Golgi network*, e.g. α2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII for substrates." (Office Action at page 6, emphasis added). The Applicants direct the Examiner to page 39, lines 23-29 of Umaña which states

> In addition, it would be valuable to *try* to re-distribute overexpressed GalT as much as possible towards the TGN *instead* of the trans-Golgi cisterna"

Id. (emphasis added).

The quoted language from Umaña is clearly speculative. Umaña does not indicate that the redistribution of GalT to the trans-Golgi network ("TGN") would necessarily result in increased ADCC. Rather, Umaña only indicates that it *might* be desirable to redistribute the GalT glycosyltransferase towards the TGN *instead* of the *trans*-Golgi cisterna. At most, this constitutes an invitation to experiment. Umaña simply does not provide the requisite reasonable expectation for successfully producing or modifying the glycosylation profile of polypeptides having increased Fc-receptor binding or effector function by the use of fusion proteins as recited in the pending claims.

Additionally, even assuming, *arguendo*, that Umaña suggests redistributing GalT activity to the *trans*-Golgi network, Umaña teaches away from redistributing GalT activity towards the trans-Golgi cisterna, which includes the *medial* Golgi. Thus, not only does Umaña fail to teach or suggest the use of host cells expressing a fusion polypeptide comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III, it also fails to teach the use of host cells expressing a fusion polypeptide comprising GalT and the Golgi localization domain of a non-TGN resident polypeptide selected from the group consisting of: Man I, Man II, GnT I, β(1,2)-N-acetylglucosaminyltransferase II, and α1-6 core fucosyltransferase.

3. Grabenhorst

Grabenhorst describes fusion glycosyltransferases having human α(1,3)-fucosyltransferase VI (FT6) catalytic activity. Grabenhorst does not teach the

redistribution of GnT III or GalT, let alone the redistribution of GnT III or GalT towards the trans-Golgi cisterna. Nor does Grabenhorst teach producing or modifying the glycosylation profile of a polypeptide to yield a modified polypeptide having increased Fc-receptor binding or effector function. Because Grabenhorst also fails to teach or suggest (i) the use of host cells expressing a fusion polypeptide comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III and (ii) the use of host cells expressing a fusion polypeptide comprising GalT and the Golgi localization domain of a non-TGN resident polypeptide selected from the group consisting of: Man I, Man II, GnT I, β(1,2)-N-acetylglucosaminyltransferase II, and α1-6 core fucosyltransferase, Grabenhorst does not cure the deficiencies of Umaña.

Additionally, Applicants submit that the combination of Umaña and Grabenhorst fails to provide a reasonable expectation for successfully using the recited fusion glycosyltransferases in mammalian host cells to produce modified polypeptides having increased Fc-receptor binding or effector function because (i) Umaña teaches away from redistributing GalT activity towards the trans-Golgi cisterna, which includes the *medial* Golgi, and (ii) neither reference can conclusively confirm that increased ADCC would necessarily result from polypeptides modified by the fusion glycosyltransferases recited in the pending claims.

4. Shields

Shields discusses the expression of the anti-HER Hu4D5 antibody in a variant CHO cell line that is deficient in specific fucosyltransferase reactions, wherein the expressed antibody has increased Fc receptor binding affinity and ADCC activity. However, Shields does not discuss the redistribution of glycosyltransferases, much less

the redistribution of GnT III or GalT. As such, Shields also does not cure the deficiencies of Umaña and Grabenhorst.

Additionally, the references combined fail to provide a reasonable expectation for successfully using the recited fusion glycosyltransferases in mammalian host cells to produce modified polypeptides having increased Fc-receptor binding or effector function.

5. Russell and Rabouille

While Russell purportedly discusses the use of heterologous Golgi localization domains to redistribute glycosyltransfersases in the plant Golgi pathway and Rabouille purportedly discusses the distribution of GnT I and Man II in the Golgi, neither reference teaches the use of (i) fusion polypeptides having GnT III activity and comprising the Golgi localization domain of a Golgi resident polypeptide other than GnT III or (ii) fusion polypeptides having GalT activity and comprising the Golgi localization domain of a Golgi resident polypeptide selected from the group consisting of: Man I, Man II, GnT I, GnT II, and FT to produce modified polypeptides having increased Fc-receptor binding or effector function in mammalian cells.

Additionally, the references combined fail to provide a reasonable expectation for successfully using the recited fusion glycosyltransferases in mammalian host cells to produce modified polypeptides having increased Fc-receptor binding or effector function.

6. Summary

The Examiner asserts that the combination of the Umaña, Grabenhorst, Shields, Russell, and Rabouille references renders the invention obvious. As explained above, the claimed methods are non-obvious because the cited references (1) do not teach

(individually or in combination) the use of fusion glycosyltransferases comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnTIII or fusion glycosyltransferases comprising GalT and the Golgi localization domain of a non-TGN resident polypeptide selected from the group consisting of: mannosidase I, mannosidase II, β(1,2)-N-acetylglucosaminyltransferase I, β(1,2)-N-acetylglucosaminyltransferase II, and α1-6 core fucosyltransferase in mammalian host cells; (2) do not provide one of skill in the art with a reason to modify the references to arrive at the claimed invention; and (3) do not provide a reasonable expectation of successfully producing a polypeptide having (i) increased Fc-receptor binding or effector function and (ii) oligosaccharides modified by the fusion glycosyltransferases recited in the pending claims. As such, Applicants submit that with regard to the pending claims the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of pending claims 30-34, 65-68, 74, 82-95, 186, 188-190, 195, and 206-212 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

7. The Evidence of the Superior Results of the Presently Claimed Methods Rebuts Any Prima Facie Case of Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established, which it has not, the unexpected superior results achieved using the recited fusion glycosyltransferases, for example, having GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III over the glycosylation modification methods described by Umaña, is sufficient to rebut the *prima facie* case of obviousness.

Applicants submit that even assuming, *arguendo*, that the combination of references cited by the Examiner rendered the claimed invention obvious, one of ordinary skill in the art would expect to observe similar Fc-receptor binding, effector functions and glycan structures of antibodies modified by the overexpression of GnT III and the claimed fusion glycosyltransferases, *i.e.*, similar FcγRIIIa binding and ADCC, and not the superior results the Applicants have observed.

Applicants' once more direct the Examiner's attention to the unexpected and superior results described in their post-filing publication, Ferrara *et al., Biotech. Bioeng. 93*:851-861 (2006) ("Ferrara"). The Examiner at page 11 of the Office Action stated that "Ferrara et al was published in 2006, and ... thus cannot provide a reason to combine the above references as of applicants filing date, or the date of the references." Applicants submit that Ferrara was not submitted to "provide a reason to combine the cited references," but as evidence that the claimed invention yields unexpectedly improved properties or properties not present in the art. Applicants direct the Examiner's attention to the M.P.E.P at § 2145, which states that rebuttal evidence and arguments can be presented in the specification, by counsel, or by way of an affidavit or declaration under 37 CFR 1.132.

Ferrara illustrates the unexpected glycan, FcγRIIIa binding, and ADCC differences observed between anti-CD20 antibodies glycoengineered in:

a) HEK293-EBNA host cells overexpressing rat GnT III;

b) HEK293-EBNA host cells expressing fusion glycosyltransferases comprising rat GnT III catalytic activity and a human Man II Golgi localization domain; and

c) HEK293-EBNA host cells expressing fusion glycosyltransferases comprising rat GnT III catalytic activity and a human GnT I Golgi localization domain.

Figure 2A and Table I of Ferrara show that the use of GnT I, GnT II, FT, or Man II localization domains in the place of a native GnT III localization domain results in an increased proportion of bisected non-fucosylated hybrid oligosaccharides (mainly *m/z* 1664) linked to the secreted antibody. The overexpression of GnT III in mammalian host cells co-expressing antibodies, on the other hand, led to the production of antibodies with lower levels of bisected non-fucosylated oligosaccharides with lower FcγRIIIa binding affinity as compared to antibodies that had been glycoengineered in host cells co-expressing fusion glycosyltransferases comprising rat GnT III catalytic domains and human Man II Golgi localization domains. *See* Ferrara at pages 856-857 and Figure 4. Applicants submit that the combined teachings of the cited references fail to demonstrate the superior Fc-receptor binding ability of polypeptides modified by the recited fusion glycosyltransferases.

Additionally, Figure 5A of Ferrara shows that antibodies modified by fusion glycosyltransferases having rat GnT III catalytic domains and human Man II Golgi localization domains have superior ADCC as compared to unmodified antibodies. Applicants submit that the combined teachings of the cited references fail to demonstrate the superior effector functions of polypeptides modified by the recited fusion glycosyltransferases.

The unexpected and superior results presented in Ferrara provide further support for the unexpected and superior results also disclosed in the present specification in Figures 11, 29, and 31. For example, Figure 11 of the specification discloses the superior ADCC properties of antibodies modified by fusion glycosyltransferases having

GnT III activity and the Golgi localization domain of Man II as compared to antibodies modified by just the overexpression of GnT III.

In summary, Applicants submit that none of the above-cited references, alone or in combination, teach or suggest such glycan structural differences or such antibody functional differences. Accordingly, these results are sufficient to rebut the *prima facie* case of obviousness

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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